

ANNEXES

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of 03.10.01

AMENDMENT

To: Examiner of the Patent Office

1. Identification of the International Application
PCT/JP00/04991

2. Applicant

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3. Item to be Amended
Claims

4. Subject Matter of Amendment

The expression " (When either R_2 or R_3 does not form, together with Z , R_1 and X , a saturated or unsaturated five- to eight-membered cyclic group, Ar is not a substituted thiazolyl group.)" should be added in the Claim 1 on page 484 (6th to 9th line).

The expression " (When either R_{2a} or R_{3a} does not form, together with Z_a , R_{1a} and X_a , a saturated or unsaturated five- to eight-membered cyclic group, Ar is not a substituted thiazolyl group.)" should be added in the Claim 2 on page 491 (23rd to 24th line) and on page 491/1 (1st to 2nd line).

The expression " (Herein, a nitrogen-containing heteroaromatic ring group does not include a quinolyl group.)" should be added in the Claim 4 on page 497 (23rd to 25th line), and the expression " (When R_{2p} does not form, together with the binding carbon atom, R_{1p} and X_p , a saturated or unsaturated five- to six-membered cyclic group, Ar is not a substituted thiazolyl group.)" should be added in the Claim 4 on page 498 (6th to 9th line).

The expression " (When either R_2 or R_3 does not form, together with Z, R_1 and X, a saturated or unsaturated five- to eight-membered cyclic group, Ar is not a substituted thiazolyl group.)" should be added in the Claim 7 on page 526 (6th to 9th line).

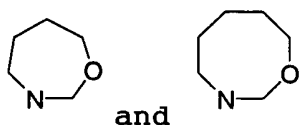
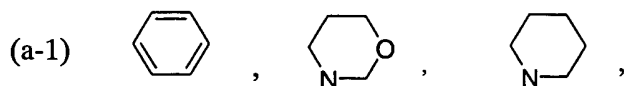
The expression " (When either R_2 or R_3 does not form, together with Z, R_1 and X, a saturated or unsaturated five- to eight-membered cyclic group, Ar is not a substituted thiazolyl group.)" should be added in the Claim 10 on page 541 (23rd to 25th line).

5. List of Attached Documents

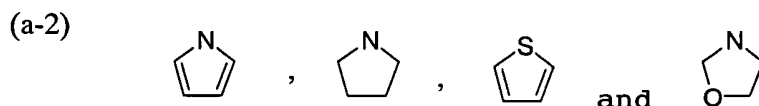
Replacement sheet of page 484 and 484/1 (Claim1); 491 and 491/1 (Claim2); 497, 497/1, 498 and 498/1 (Claim4); 526 and 526/1 (Claim7); and 541 and 541/1 (Claim10)

alkanoylamidino lower alkyl group, a lower alkylsulfinyl group, a lower alkylsulfonyl group, a lower alkylsulfonylamino group, a hydroxyimino group and a lower alkoxyimino group, and a substituent selected from groups
 5 represented by the formula $Y_1-W_1-Y_2-R_p$ (wherein: R_p , W_1 , Y_1 and Y_2 have the same meanings as stated above) (When either R_2 or R_3 does not form, together with Z , R_1 and X , a saturated or unsaturated five- to eight-membered cyclic group, Ar is not a substituted thiazolyl group.); R_4 and R_5
 10 are each, the same or different, a hydrogen atom, halogen atoms, a hydroxy group, an amino group, or a substituent represented by the formula $Y_3-W_2-Y_4-R_s$ (wherein: R_s , W_2 , Y_3 and Y_4 have the same meanings as stated above), or any of a lower alkyl group, an aryl group or an aralkyl group which
 15 may be substituted with one to three of the same or different substituent(s) selected from both a set of groups consisting of a lower alkyl group, a cyano group, a nitro group, a carboxyl group, a carbamoyl group, a formyl group, a lower alkanoyl group, a lower alkanoyloxy group, a
 20 hydroxy lower alkyl group, a cyano lower alkyl group, a halo lower alkyl group, a carboxy lower alkyl group, a carbamoyl lower alkyl group, lower alkoxy group, a lower alkoxy carbonyl group, lower alkoxy carbonylamino group, a lower alkoxy carbonylamino lower alkyl group, a lower
 25 alkyl carbamoyl group, a di-lower alkyl carbamoyl group, a carbamoyloxy group, a lower alkyl carbamoyloxy group, di-lower alkyl carbamoyloxy group, an amino group, a lower alkylamino group, a di-lower alkylamino group, a tri-lower alkylammonio group, an amino lower alkyl group, a lower

alkylamino lower alkyl group, a di-lower alkylamino lower alkyl group, a tri-lower alkylammonio lower alkyl group, a lower alkanoylamino group, an aroylamino group, a lower



and



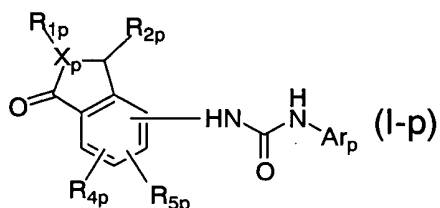
which may have one or more kinds of hetero atom(s), and
 5 which may be substituted with one to three of the same or
 different substituent(s) selected both from a set of groups
 consisting of a lower alkyl group, a spiro cyclo lower
 alkyl group which may be substituted, a hydroxy group, a
 hydroxy lower alkyl group, lower alkoxy group, a lower
 10 alkoxy carbonyl group, a lower alkoxy carbonylamino group, a
 lower alkoxy carbonylamino lower alkyl group, a lower
 alkyl carbamoyl group, a lower alkyl carbamoyloxy group, a
 lower alkylamino group, a di-lower alkylamino group, an
 amino lower alkyl group, a lower alkylamino lower alkyl
 15 group, a di-lower alkylamino lower alkyl group, a lower
 alkanoylamino group and an aroylamino group, and groups
 represented by the formula $Y_{1a}-W_{1a}-Y_{2a}-R_{pa}$ (wherein: R_{pa} , W_{1a} ,
 Y_{1a} and Y_{2a} have the same meanings as stated above), and,
 furthermore, which may be fused with a cyclo lower alkyl
 20 group, an aryl group, a heteroaromatic ring group selected
 from a group of a pyridyl group and a pyrazolyl group, and
 an aliphatic heterocyclic group selected from a group of
 piperidinyl group and a pyrrolidinyl group (When either R_{2a}
 or R_{3a} does not form, together with Z_a , R_{1a} and X_a , a

saturated or unsaturated five- to eight-membered cyclic group, Ar is not a substituted thiazolyl group.); R_{4a} and R_{5a} are each, the same or different, a hydrogen atom or a

or a lower alkyl group, an aryl group or an aralkyl group which may be substituted with one to three of the same or different substituent(s) selected from a set of groups consisting of substituents comprising any of a hydrogen atom, halogen atoms or a substituent represented by the
 5 formula $Y_{3b}-W_{2b}-Y_{4b}-R_{sb}$ (wherein: R_{sb} , W_{2b} , Y_{3b} and Y_{4b} have the same meanings as stated above), or a substituent selected from a set of groups consisting of a lower alkyl group, a hydroxy lower alkyl group, a halo lower alkyl group, a
 10 lower alkoxycarbonylamino group, a lower alkoxycarbonylamino lower alkyl group, a lower alkylcarbamoyl group, a lower alkylamino group, a lower alkylamino lower alkyl group, a lower alkanoylamino group, and an aroylamino group,; and the formula $---$ means a
 15 single bond or a double bond.

4. A compound according to any one of claim 1 to claim 3, having a structure of Formula (I-p) and pharmaceutically acceptable salts thereof,

20 Formula (I-p)



wherein: Ar_p is a nitrogen-containing heteroaromatic ring group which may be substituted (Herein, a nitrogen-containing heteroaromatic ring group does not include a
 25 quinolyl group.), X_p is a carbon atom (CH) or a nitrogen atom, R_{1p} is a hydrogen atom or a lower alkyl group which

may be substituted, R_{2p} is a hydrogen or an oxo group (which forms carbonyl group, together with the carbon

atom on which it stands), or forms, together with the carbon atom on which it stands, R_{1p} and X_p , a saturated or an unsaturated five- or six-membered cyclic group which may have one or more kinds of hetero atom(s) selected from a group of a nitrogen atom and a sulfur atom or which may be substituted (When R_{2p} does not form, together with the binding carbon atom, R_{1p} and X_p , a saturated or unsaturated five- to six-membered cyclic group, Ar is not a substituted thiazolyl group.); R_{4p} and R_{5p} are each, the same or different, any of a hydrogen atom, halogen atoms, a hydroxy group, an amino group or a lower alkyl group, an aryl group or an aralkyl group which may be substituted.

5. A compound according to claim 1, wherein the compound is

15 N'-(pyrrolidino[2,1-b]isoindolin-4-on-8-yl)-N-(5-(2-octylaminomethyl)pyrazol-3-yl)urea, N'-(pyrrolidino[2,1-b]isoindolin-4-on-8-yl)-N-(5-(2-methyl-4,4-dimethylpentylaminomethyl)pyrazol-3-yl)urea, N'-(pyrrolidino[2,1-b]isoindolin-4-on-8-yl)-N-(5-(5-methoxyindan-2-ylaminomethyl)pyrazol-3-yl)urea,

20 N'-(pyrrolidino[2,1-b]isoindolin-4-on-8-yl)-N-(5-(2-methylindan-2-ylaminomethyl)pyrazol-3-yl)urea, N'-(pyrrolidino[2,1-b]isoindolin-4-on-8-yl)-N-(5-(5-chloroindan-2-ylaminomethyl)pyrazol-3-yl)urea, N'-(pyrrolidino[2,1-b]isoindolin-4-on-8-yl)-N-(5-(6-methylpyridin-2-yl)pyrazol-3-yl)urea, N'-(pyrrolidino[2,1-b]isoindolin-4-on-8-yl)-N-(5-(pyrrolidin-2-yl)pyrazol-3-yl)urea, N'-(pyrrolidino[2,1-b]isoindolin-4-on-8-yl)-N-(5-(t-butylaminomethyl)pyrazol-3-yl)urea, N'-(pyrrolidino[2,1-

b]isoindolin-4-on-8-yl)-N-(5-(pyrazolo[5,4-b]pyridin-3-yl)urea, N'-(pyrrolidino[2,1-b]isoindolin-4-on-8-yl)-N-(5-(1-hydroxymethylcyclopentylaminomethyl)pyrazol-3-yl)urea,

group, a lower alkylsulfonyl group, a lower alkylsulfonylamino group, a hydroxyimino group and a lower alkoxyimino group, and a substituent or substituents selected from groups represented by the formula $Y_1-W_1-Y_2-R_p$ (wherein: R_p , W_1 , Y_1 and Y_2 have the same meanings as stated above) (When either R_2 or R_3 does not form, together with Z , R_1 and X , a saturated or unsaturated five- to eight-membered cyclic group, Ar is not a substituted thiazolyl group.); R_4 and R_5 are each, the same or different, a hydrogen atom, halogen atoms, a hydroxy group, an amino group, or a substituent represented by the formula $Y_3-W_2-Y_4-R_s$ (wherein: R_s , W_2 , Y_3 and Y_4 have the same meanings as stated above), or any of a lower alkyl group, an aryl group or an aralkyl group which may be substituted with one to three of the same or different substituent(s) selected from both a set of groups consisting of a lower alkyl group, a cyano group, a nitro group, a carboxyl group, a carbamoyl group, a formyl group, a lower alkanoyl group, a lower alkanoyloxy group, a hydroxy lower alkyl group, a cyano lower alkyl group, a halo lower alkyl group, a carboxy lower alkyl group, a carbamoyl lower alkyl group, lower alkoxy group, a lower alkoxycarbonyl group, lower alkoxycarbonylamino group, a lower alkoxycarbonylamino lower alkyl group, a lower alkylcarbamoyl group, a di-lower alkylcarbamoyl group, a carbamoyloxy group, a lower alkylcarbamoyloxy group, di-lower alkylcarbamoyloxy group, an amino group, a lower alkylamino group, a di-lower alkylamino group, a tri-lower alkylammonio group, an amino lower alkyl group, a lower alkylamino lower alkyl group, a

di-lower alkylamino lower alkyl group, a tri-lower alkylammonio lower alkyl group, a lower alkanoylamino group, an aroylamino group, a lower alkanoylamidino lower alkyl

substituted, a hydroxyl group, a cyano group, halogen atoms, a nitro group, a carboxyl group, a carbamoyl group, a formyl group, a lower alkanoyl group, a lower alkanoyloxy group, a hydroxy lower alkyl group, a cyano lower alkyl group, a halo lower alkyl group, a carboxy lower alkyl group, a carbamoyl lower alkyl group, lower alkoxy group, a lower alkoxycarbonyl group, lower alkoxycarbonylamino group, a lower alkoxycarbonylamino lower alkyl group, a lower alkylcarbamoyl group, a di-lower alkylcarbamoyl group, a carbamoyloxy group, a lower alkylcarbamoyloxy group, di-lower alkylcarbamoyloxy group, an amino group, a lower alkylamino group, a di-lower alkylamino group, a tri-lower alkylammonio group, an amino lower alkyl group, a lower alkylamino lower alkyl group, a di-lower alkylamino lower alkyl group, a tri-lower alkylammonio lower alkyl group, a lower alkanoylamino group, an aroylamino group, a lower alkanoylamidino lower alkyl group, a lower alkylsulfinyl group, a lower alkylsulfonyl group, a lower alkylsulfonylamino group, a hydroxyimino group and a lower alkoxyimino group, and a substituent selected from groups represented by the formula $Y_1-W_1-Y_2-R_p$ (wherein: R_p , W_1 , Y_1 and Y_2 have the same meanings as stated above) (When either R_2 or R_3 does not form, together with Z , R_1 and X , a saturated or unsaturated five- to eight-membered cyclic group, Ar is not a substituted thiazolyl group.); R_4 and R_5 are each, the same or different, a hydrogen atom, halogen atoms, a hydroxy group, an amino group, or a substituent represented by the formula $Y_3-W_2-Y_4-R_s$ (wherein: R_s , W_2 , Y_3 and Y_4 have the same meanings as stated above), or any of a

lower alkyl group, an aryl group or an aralkyl group which may be substituted with one to three of the same of different substituent or substituents selected from both a